Steven J Lichtenstein[1]
David B Granet[2]

[1]Associate Clinical Professor of Pediatrics and Surgery, University of Illinois College of Medicine at Peoria and Chicago, Peoria, IL, USA,
[2]Anne F. Ratner Professor of Ophthalmology and Pediatrics, University of California at San Diego, San Diego, CA, USA

Fluoroquinolones compared to 1% azithromycin in DuraSite® for bacterial conjunctivitis

In a recent issue of *Clinical Ophthalmology*, Friedlaender and Protzko (2007) review the development and efficacy of 1% azithromycin in DuraSite® (AzaSite™, Inspire Pharmaceuticals, Inc., Durham, NC) for the treatment of bacterial conjunctivitis. The authors conclude that 1% azithromycin in DuraSite offers a simplified dosing regimen with sustained bactericidal levels that decrease resistance development. While 1% azithromycin in DuraSite is a new formulation of azithromycin that allows topical ocular use, azithromycin and DuraSite have been around for many years. Evidence demonstrates a greater potential for emerging resistance with azithromycin, an older drug, especially when formulated in a vehicle that prolongs low levels of antibiotic exposure over time.

Azithromycin is derived from the parent class of macrolides, known to be bacteriostatic. The ability of azithromycin to achieve high intracellular concentrations compared with other macrolides is credited for its bactericidal activity. However, in clinical practice, given the high level of Gram-positive resistance patterns, azithromycin demonstrates time-dependent, bacteriostatic kill against most bacteria within its clinical spectrum. DuraSite technology allows azithromycin to stay in contact with the ocular surface longer than conventional aqueous eye drops; a potential concern for resistance that led to a US Food and Drug Administration (FDA) warning on their package insert regarding missing doses: "Skipping doses or not completing the full course of therapy may … increase the likelihood that bacteria will develop resistance and will not be treatable by AzaSite (azithromycin ophthalmic solution) or other antibiotic drugs in the future." (Azasite 2007). In contrast, potent, rapid-killing, broad-spectrum topical anti-infectives are less likely to promote resistance and do not carry such an FDA warning. Among these agents are the ophthalmic fourth-generation fluoroquinolones (FQs) that demonstrate concentration-dependent bactericidal kill and are not reliant on time as suggested by the authors.

The authors state that changing trends in the activity of newer-generation FQs demonstrate increased resistance among common bacterial conjunctivitis pathogens such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. However, within the article, all 3 cited references (Goldstein et al 1999; Venezia et al 2001; Ambrose et al 2004) document resistance patterns in older-generation FQs instead of newer fourth-generation agents such as moxifloxacin 0.5% and gatifloxacin 0.3%. The distinction is critical. The development of resistance to older FQs develops through a single-step topoisomerase mutation (topoisomerase II or topoisomerase IV). However, resistance to newer FQs requires 2 spontaneous mutations at both topoisomerase II and topoisomerase IV and occurs much less frequently (Hwang 2004). In fact, in isolates of *S. aureu*s, *S. pneumoniae*, and *H. influenzae* from conjunctivitis patients seen in a community practice setting, resistance to a fourth-generation agent, moxifloxacin, was not observed (Ohnsman et al 2007).

This study showed that only when combined with extra vehicle drops (likely containing preservative) for a total of 4 applications per day could 1% azithromycin in DuraSite (dosed twice daily for the first 2 days, then daily for 3 days) achieve a success profile similar to tobramycin dosed four times daily for 5 days. Since the clinical resolution rate of 1% azithromycin in DuraSite dosed in combination with

Correspondence: Steven J Lichtenstein
Associate Clinical Professor of Pediatrics and Surgery, University of Illinois College of Medicine at Peoria and Chicago, Peoria, IL, USA
Tel +1 309 243 2400
Email eyedoc44@aol.com

13 drops of vehicle (total of 20 drops) in the comparative tobramycin study was higher (79.9%) than reported in the comparative vehicle study (63.1%) with only 7 drops of azithromycin, it is probable that the numerous extra drops of vehicle created a washout effect or provided some antibacterial activity. In fact, given that the 2 arms of the study were performed simultaneously, the data indicate that without the 13 extra washout drops of vehicle, azithromycin would not have even reached equivalence to tobramycin.

Furthermore, a numerical advantage and statistical trend toward greater bacterial eradication with 0.3% tobramycin (94.3%) compared with 1% azithromycin in DuraSite (88.1%) ($p = 0.073$) was observed, although there was no overall difference in the rate of clinical resolution at the test-of-cure visit on Day 6 between agents; a finding we suggest may be related to the self-limiting nature of the disease. High failure rates of bacterial eradication (ie, resistant isolates of *S. aureus* and *S. pneumoniae* 50% and 40%, respectively) were observed as were lower rates of overall clinical resolution (70.6% and 85.5%, respectively) in all patients infected with azithromycin-resistant isolates.

Clinicians should consider the speed in which a therapy eradicates infection, the anticipated spectrum of activity, tolerability, compliance, and cost of therapy when choosing empiric antibiotic therapy. While 1% azithromycin in DuraSite offers the perceived advantage of fewer doses, equivalence to tobramycin was only reached by administering 1 drop of 1% azithromycin in DuraSite with 3 drops of vehicle (ie, 4 drops) in the eye each day, questioning the overall efficacy of a true once-daily regimen. Also disconcerting is this agent's potential to select for resistant pathogens that can be transmitted to the fellow eye of the patient or to other close contacts as warned by the FDA in the package insert. Furthermore, less frequent dosing does not always translate into increased compliance. If a therapy is not tolerable, the benefit of less frequent dosing may not be realized. In a recently completed study, the fourth-generation FQ, moxifloxacin 0.5%, was found to be more comfortable, resulted in less blurring, and was preferred (84% to 16%) over 1% azithromycin in DuraSite (Granet et al 2007).

After reviewing the data from the authors presented in their article we must disagree that 1% azithromycin in DuraSite "appears more favorable than the currently available choices in the UK and US." When clinicians consider all factors related to therapy (eg, bacterial resistance, blurriness, dosing compliance, and comfort) we suggest rapid-killing bactericidal agents such as ophthalmic fourth-generation fluoroquinolones are better options for the treatment of conjunctivitis.

References

Ambrose PG, Blast D, Doern CV, et al. 2004. Fluoroquinolone-resistant streptococcus pneumoniae, an emerging but unrecognized public health concern: is it time to resight the goal post? *Clin Infect Dis*, 39:1554–6.

AzaSite. 2007. AzaSite Package Insert. Durham, NC:Inspire Pharmaceuticals, Inc [online]. Accessed November 8th, 2007. URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

Friedlaender MH, Protzko E. 2007. Clinical development of 1% azithromycin in DuraSite®, a topical azalide anti-infective for ocular surface therapy. *Clin Ophthalmol*, 1:3–10.

Goldstein MH, Kowalski RP, Gordan YJ. 1999. Emerging fluoroquinolone resistance in bacterial keratitis: a 5-year review. *Ophthalmology*, 106:1313–18.

Granet DB, Lichtenstein SJ, Onofrey B, et al. 2007. An assessment of the tolerability of moxifloxacin 0.5% compared to azithromycin 1.0% in DuraSite®. *Clin Ophthalmol*, 1:519–25.

Hwang DG. 2004. Fluoroquinolone resistance in ophthalmology and the potential role for newer ophthalmic fluoroquinolones. *Surv Ophthalmol*, 49(suppl):S79–83.

Ohnsman C, Ritterband D, O'Brien T, et al. 2007. Comparison of azithromycin and moxifloxacin against bacterial isolates causing conjunctivitis. *Curr Med Res Opin*, 23:2241–9.

Venezia RA, Domarack BE, Evans AM, et al. 2001. Selection of high-level oxacillin resistance in heteroresistant Staphylococcus aureus by fluoroquinolone exposure. *J Antimicrob Chemother*, 48:375–81.

Response to correspondence from Lichtenstein and Granet Re: Fluoroquinolones compared to 1% azithromycin in DuraSite® for bacterial conjunctivitis

Mitchell H Friedlaender[1]
Eugene Protzko[2]

[1]Division of Ophthalmology, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla, CA, 92037 USA; [2]Seidenberg Protzko Eye Associates, 930 Revolution St, Havre De Grace, MD, 21014 USA

In our review of the development and efficacy of 1% azithromycin in DuraSite® (AzaSite™, InSite Vision, Alameda, CA, USA) published in *Clinical Ophthalmology* (Friedlaender and Protzko 2007), we describe azithromycin as a well known anti-infective agent with pharmacokinetic properties that were not sufficiently exploited for topical use in the eye until the development of AzaSite. A sustained release ocular antibiotic, AzaSite delivers sufficiently high concentrations of azithromycin to the eye to eradicate common causative pathogens of bacterial conjunctivitis. The means by which azithromycin is delivered to the eye in the AzaSite formulation gives it much greater tissue concentrations than expected.

The DuraSite vehicle completely solubilizes azithromycin in a matrix that stays in contact with the ocular surface longer than conventional aqueous drops. A full course of therapy of AzaSite for bacterial conjunctivitis requires only 9 drops. Drs Lichtenstein and Granet (2007) suggest that this is a potential concern for the development of drug resistance and it is also the reason why the US Food and Drug Administration (FDA) places a warning about skipping doses on the package insert.

We would like to point out that, regardless of the anti-infective used, the misuse of an antibiotic – including failure to complete therapy, skipping doses, or reuse of leftover antibiotic – may expose patients to the development of bacterial resistance. Warnings of this nature appear on the patient information inserts for a variety of antibiotics, including Avelox® (oral moxifloxacin). The guidance in the patient counseling section of AzaSite's prescribing information is reflective of the FDA's acknowledgement of widespread antibiotic misuse and new requirements for labeling.

Aside from these matters of newer packaging guidelines, the potential for the development of resistance with topical 1% azithromycin in DuraSite is minimized by its newer delivery method and by azithromycin's affinity for tissue, resulting in high concentrations of drug in tears and conjunctiva. During the pivotal trials for 1% azithromycin in DuraSite, no indication of the development of resistance to azithromycin was observed. MICs of cultured bacteria did not increase during treatment with AzaSite. Furthermore, in the vehicle trial, AzaSite effectively eradicated 85% (23/27) of azithromycin-resistant pathogens.

Pivotal trials for AzaSite were conducted in patients with bacterial conjunctivitis, which commonly presents as a self-limited disease but may be severe in some cases. The value of drug intervention to eradicate bacteria and speed resolution of the signs and symptoms must be measured at an early phase in the disease process in order to assess the efficacy of treatment. We reject the suggestion that the high rate of clinical cure measured at day 6 in the AzaSite pivotal trial was related to the self-limited nature of the disease.

In support of this, we point out that a comparison of clinical cure (resolution of all signs and symptoms) achieved with moxifloxacin and azithromycin yields highly similar results at the end of a 5-day dosing period – and in both cases the rates are significantly better than with vehicle – refuting the notion that by day 6 clinical cure rates would have improved without intervention. AzaSite attained the same level of clinical cure as moxifloxacin with 50% fewer active drops. Patients in the phase 3 trials for moxifloxacin were dosed three times a day for 4 days. Compared to vehicle, the difference in the rate of clinical cure was significant at day 5 but not at the test-of-cure on day 9, when according to most clinical accounts the symptoms had begun to resolve on their own (Table 1). The rate of bacterial eradication (82%) was measured at day 9 in the moxifloxacin group, compared to 89% on Day 6 + 1 in the AzaSite trial.

Lack of susceptibility to fourth-generation fluoroquinolones in vitro was reported in the AzaSite clinical trials. Although the number of instances was small, more than 50% of these fluoroquinolone-resistant isolates were susceptible to AzaSite. Recent clinical and epidemiologic studies have also reported resistance to the new fourth-generation fluoroquinolones, including moxifloxacin. In addition to the findings in the AzaSite clinical trials, reports of 4th generation fluroquinolone resistant bacteria have been growing in number as reported in bacterial keratitis and following cataract surgery, and refractive surgery (Jhanji et al 2007; Mamalis 2007; Melo et al 2007; Ta and Sahm 2007).

Smart use of the appropriate antibiotic is the key to controlling the spread of resistance (CDC 2006). Fourth generation fluoroquinolones are powerful drugs, but declining in vitro susceptibility as measured over the past 5 years has important implications for their use in relatively mild infections such as uncomplicated conjunctivitis or chronic infections such as blepharitis (Miller et al 2006; Mamalis 2007). A systematic meta-analysis of antibiotic misuse by Kardas and colleagues (2005) concludes that patient education and simpler antibiotic regimens should be encouraged to promote responsible use of antibiotic therapy. Most antibacterial eye drops currently available require 3 to 8 doses daily for 7 to 10 days, a demanding dosing schedule that can result in missed doses and unfinished courses of therapy (Kernt

Table 1 Clinical cure of bacterial conjunctivitis in 0.5% moxifloxacin vs. vehicle in phase 3 clinical trial (FDA 2003)*

	Cumulative	% Clinical cure		p value
	Drops; No.	Moxifloxacin	Vehicle	
Day 3	9	27	15	0.0186
Day 5 (end-of-therapy)	15	66	51	0.0096†
Day 9 (test-of-cure)	15	83	74	0.0991

Notes: *Data are from modified intent-to-treat population and includes all patients who met inclusion criteria, received treatment, had at least 1 follow up visit, and were culture-positive for bacteria on day 1; †$p < 0.05$.

et al 2005). AzaSite is recommended for dosing twice daily on the first two days of treatment, followed by once-daily dosing on days 3 through 7. In interviews of 141 patients, Kass and colleagues (1982) concluded that simplifying patient instruction and dosing schedules for eye drops would improve compliance. With twice-daily dosing for the first two days and simple once-daily dosing for the remainder of the treatment period, AzaSite simplifies the regimen normally associated with antibiotic eye drops.

A patient's level of adherence to an appropriate anti-infective treatment regimen is a key variable in curing acute bacterial infections. Adherance can be difficult for some patients to maintain and even more difficult for healthcare providers to measure (Schwartz et al 2004). This was demonstrated in the comparative tolerability study by Dr. Granet and colleagues (2007). Their study comparing assessments of Vigamox and AzaSite in healthy patients was not fully masked, and highly dependent on subjective descriptions of tolerability. The introduction of investigator bias in this type of study cannot by ruled out.

Most potent eye drops are associated with some transient sensations when they are first instilled and it is incorrect to label these sensations as "adverse events". Loss of vision, glaucoma, and allergic reactions would be considered "adverse events" by most standards. The symptoms categorized as "adverse events" by Granet and colleagues (2007), would not. In two much larger studies, which were double-masked, we described transient symptoms, such as burning, stinging, and itching which were not statistically different in the AzaSite and vehicle groups. Furthermore, these were double-masked studies in inflamed red eyes which should have been highly sensitive to irritants.

Once-daily dosing of eye drops has been associated with enhanced patient compliance, which minimizes the potential for the development of resistant organisms. As a result, short and convenient means of treating ocular infection is essential to improve compliance, outcome, and minimize the potential for the development of resistance.

References

[CDC] Centers for Disease Control and Prevention. 2006. About antibiotic resistance: Why are bacteria becoming resistant to antibiotics? Centers for Disease Control and Prevention. April 21, 2006 [online]. Accessed November 29, 2007. URL: http://www.cdc.gov/drugresistance/community/anitbiotic-resistance.htm#4.

Friedlaender MH, Protzko E. 2007. Clinical development of 1% azithromycin in DuraSite®, a topical azalide anti-infective for ocular surface therapy. *Clin Ophthalmol*, 1:3–10.

Granet DB, Lichtenstein SJ, Onofrey B, et al. 2007. An assessment of the tolerability of moxifloxacin 0.5% compared to azithromycin 1.0% in DuraSite®. *Clin Ophthalmol*, 1:519–25.

Jhanji V, Sharma N, Satpathy G, et al. 2007. Fourth-generation fluoroquinolone-resistant bacterial keratitis. *J Cataract Refract Surg*, 33:1488–9.

Kardas P, Devine S, Golembesky A, et al. 2005. A systematic review and meta-analysis of misuse of antibiotic therapies in the community. *Int J Antimicrob Agents*, 26:106–13.

Kass MA, Hodapp E, Gordon M, et al. 1982. Part I. Patient administration of eye drops: interview. *Ann Ophthalmol*, 14:775–9.

Kernt K, Martinez MA, Bertin D, et al. 2005. A clinical comparison of two formulations of tobramycin 0.3% eye drops in the treatment of acute bacterial conjunctivitis. *Eur J Ophthalmol*, 15:541–9.

Mamalis N. 2007. From The Editor: The increasing problem of antibiotic resistance. *J Cataract Refract Surg*, 33:1831–2.

Melo GB, Höfling-Lima AL, Bispo PJM, et al. 2007. Susceptibility of coagulase-ngative Staphylococcus to moxifloxacin and gatifloxacin isolated from culture-proven endophthalmitis. Poster presented at: Annual Meeting of Association for Research in Vision and Ophthalmology. May 6–10, 2007; Fort Lauderdale, FL. Poster B392.

Miller D, Flynn PM, Scott IU, et al. 2006. In vitro fluoroqunolone resistance in staphylococcal endophthalmitis. *Arch Ophthalmol*, 124:479–83.

Schwartz DB, Adler A, Dasaro AP, et al. 2004. Improving adherence with antimicrobial therapy for reiratory tratct infections: A discussion of directly observed therapy (DOT) and short-sourse therapies. *Am J Therap*, 11:S18–S21.

Ta CN, Sahm DF; for the Ocular TRUST. 2007. Antimicrobial susceptibility patterns in MRSA vs MSSA eye infection: results from Ocular TRUST. Poster presented at: Annual Meeting of Association for Research in Vision and Ophthalmology. May 6–10, 2007; Fort Lauderdale, FL. Poster B772.

U.S. Food and Drug Association. Center for Drug Evaluation and Research. 2007. NDA 21–598. Medical review(s) [of moxifloxacin hydrochloride ophthalmic solution, 0.5%]. April 15, 2003 [online]. Accessed April 30, 2007. URL: http://www.fda.gov/cder/foi/nda/2003/021493_Zymar.htm.